REMARKS/ARGUMENTS

Status of the Specification

The specification stands objected to with regard to the "Table of Contents." Applicants have amended the specification to eliminate the "Table of Contents." Applicants note that the substitute specification did not set forth the Table of Contents. Accordingly, Applicants respectfully request that the above objection be withdrawn.

The specification was also amended to set forth cleavable peptide subject matter set forth in U.S. Patent No. 5,457,066 (*see,* col. 1 lines 60-65; *see,* col. 2 last full paragraph, and *see*, paragraph bridging cols. 2 and 3) which was incorporated by reference in the instant application at p. 24, line 21 by operation of the recital at page 33, last line. Accordingly, Applicants believe the amendments to the specification add no new matter and respectfully request their entry.

Status of the Claims

Claims 98 to 104, 109 to 111, 114 to 124, 129 to 131, 134 to 144 were previously pending and presented for examination. Claims 99 to 101, 119 to 122, 138 to 140, 143 and 144 are canceled herein without prejudice. Claims 145 and 146 are newly presented. All the claims except for claims 116 to 118, 136, 137, 141 and 142 were amended. After entry of these amendments, claims 98, 102 to 104, 109 to 111, 114 to 118, 123, 124, 129 to 131, 129 to 131, 134 to 137, 141, 142, 145, and 146 will be pending.

Claims 98 to 104, 109 to 111, 114 to 115, 119 to 124, 129 to 131, 134 to 137, 135, 138 to 140, 143, and 144 stand objected to as allegedly unclear for reciting the term "peptidyl".

Claims 98 to 104, 109 to 111, 114 to 124, 129 to 131, and 134 to 144 stand rejected as alleged directed toward non-statutory subject matter.

Claims 98 to 104, 109 to 111, 114 to 124, 129 to 131 and 134 to 144 stand rejected as allegedly not fully enabled pursuant to 35 U.S.C. §112, first paragraph.

Claims 98 to 104, 109 to 111, 114 to 124, 129 to 131 and 134 to 144 stand rejected as allegedly not satisfying the written description requirement pursuant to 35 U.S.C. §112, first paragraph.

Claim 98 stands rejected as allegedly indefinite in view of the recital of "the bioactive conformation."

The Applicants respectfully respond to these Objections and Rejections below.

Amendments to the Claims

The claims were amended to replace each recital of "peptidyl" by "peptide" as suggested by the Examiner.

The claims were also amended to replace the recital of a "second peptidyl fragment" by a "human insulin precursor peptide fragment." Support for this subject matter is found inter alia in the previous versions of the affected claims.

Support for the amendments is indicated below according to where such may be found in the original specification rather than the substitute specification (which differs in its pagination).

Claim 98 was amended to recite "recombinant" as suggested by the Examiner. Claim 98 was further amended to set forth first peptide subject according to previous claim 140. Claim 98 was further amended to set forth human insulin precursor peptidyl fragment subject matter according to previous claim 111. Claim 98 was further amended to set forth that the first peptide fragment is capable of mediating, upon contacting of the chimeric protein with a chaotropic agent, the formation of a correctly folded conformation of the human insulin precursor peptide fragment. Support for this subject matter is found *inter alia* in the specification in the paragraph bridging pages 26 and 27.

Claim 98 was also amended to set forth that the first peptide fragment and the human insulin precursor peptide fragment may be linked by the amino acids arginine or lysine as well as the cleavable peptide fragment. Support for this subject matter is found *inter alia* in previous claim 114.

Claim 104 and 124 were amended to set forth a first peptide fragment length from 20 to 49 residues in length. Support for this subject matter is found in previous claim 139.

Claims 109, 110, 129 and 130 were amended to conform its recitals with the amended antecedents of the human insulin precursor fragment. Support for such subject matter is found *inter alia* in the previous version of these claims.

Claims 111 and 31 were amended for purposes of clarity and to conform with changes in the human insulin precursor peptide antecedent. Support for such subject matter is found *inter alia* in the previous version of these claims.

Claims 114 and 134 were amended to conform with the amendments to its antecedent in the base claim. Support for such subject matter is found *inter alia* in the previous version of the claim.

New claims 145 and 146 are respectively drawn in part to nucleic acids encoding or cells expressing chimeric proteins of SEQ ID No:6 and SEQ ID NO:7. Support for such is found as set forth previously for claims 136 and 137.

In view of the above, the Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to the Objection to Claims 98 to 104, 109 to 111, 114 to 115, 119 to 124, 129 to 131, 134, 135, 138 to 140, 143, and 144 for alleged lack of clarity.

Without acquiescing to the position of the Examiner, and in order to facilitate examination of the application, the Applicants have amended the claims as suggested by the Examiner to recite "peptide" in place of "peptidyl." Accordingly, the Applicants request that the objection be withdrawn.

Response to the rejection of claims 98 to 104, 109 to 111, 114 to 124, 129 to 131, and 134 to 144 as alleged drawn to non-statutory subject matter pursuant to 35 U.S.C. §101.

Without acquiescing to the position of the Examiner, and in order to facilitate examination of the application, the Applicants have amended the base claim to recite

"recombinant" as suggested by the Examiner. Accordingly, the Applicants request that the rejection be withdrawn.

Response to the rejection of claims 98 to 104, 109 to 111, 114 to 124, 129 to 131 and 134 to 144 as allegedly lacking enablement pursuant to 35 U.S.C. §112, first paragraph.

The Examiner rejected the claims with respect to the first and second peptide fragments. The enablement of each fragment is addressed in turn.

The First Peptide Fragment

The Applicants have herein amended the base claim to recite first peptide subject matter similar to that allowed in the parent application:

Standard of Review

As noted by the Examiner, whether undue experimentation[1] is required to practice an invention is typically determined by evaluating: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Applicants address each of these factors and the Examiner's concerns as to each in turn.

i. Relative Skill of those in the Art.

Applicants submit that the relative skill of those in the art of recombinant proteins and peptide manufacture is high. Typically, such practitioners have doctoral degrees in the relevant fields. The competence of such practitioners is evidenced in U.S. Patent No. 5,719,021 to Inouye and Inouye et al. Enzymes 45:314-321 (1991)(both references cited by the Examiner) and the other references already of record.

[1] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue'; not 'experimentation' " in determining whether pending claims are enabled. *In re: Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

ii. Nature of the Invention.

The field of the invention is in the pharmaceutical arts and more particularly the *manufacture* of correctly folded recombinant peptides. In the pharmaceutical arts, it is routine to screen a large number of agents for their biological activity. Herein, the relevant biological activity is an intramolecular chaperone activity. The candidate first peptidyl fragments can be screened *in vitro* for their ability to increase the yield of a correctly folded recombinant insulin peptide. Insulin is one of the oldest and most studied peptide hormones.

iii. Breadth of the Claims.

Base claim 98 recites in part " an N-terminal ~~a~~ first peptide fragment of from 20 amino acids in length to 92 amino acids in length and having an amino acid sequence which is identical to an N-terminal amino acid sequence of SEQ ID NO: 2 of the same length as the first peptidyl fragment or having an amino acid sequence which differs by one or two residues from the N-terminal sequence of SEQ ID NO:2 of the same length;

...

wherein the first peptide fragment is capable of mediating, upon contacting of the chimeric protein with a chaotropic agent, the formation of a correctly folded conformation of the human insulin precursor.

Thus, the first peptidyl subject matter is constrained to first peptidyl fragments having from 20 to 92 amino acids and varying in amino acid sequence from a corresponding sequence set forth in SEQ ID NO:2 by only 0, 1, or 2 residues.

iv. Amount of Guidance Presented.

Applicants teach all the methods required to practice the claimed subject matter. The specification teaches methods of making such subject matter at pp. 22-23, of testing such first peptidyl fragments for their intramolecular chaperone activity in Section 4.5 beginning on p. 28) and exemplifies such in the Examples. The specification teaches how to obtain, purify and characterize a resulting correctly folded human insulin in Sections 5.5 through 5.6, respectively. Moreover, as recited in the MPEP §2164.01 "A patent need not teach, and preferably omits, what is well known in the art." Inouye (see U.S. Patent No. 5,719,021; already of record) also more

generally teaches standard methods which one of ordinary skill in the art could readily adapt in order to practice the invention.

v. Presence of Working Examples.

The specification provides working examples based upon using a 49 amino acid long intramolecular chaperone first peptidyl sequence and a correctly folded insulin precursor of the claims. The inventor's affidavit, as filed in the parent, evidenced the suitability of a 40-mer first peptidyl fragment and the unsuitability of an 18-mer first peptidyl fragment. Thus, the ability to make and identify suitable and unsuitable first peptidyl fragments is demonstrated.

vi. State of the Art.

The art of making and testing variant intramolecular chaperone peptides is substantially more advanced than the Office Action sets forth. Inouye in U.S. Patent No. 5,719,021 helps to illustrate the advanced state of the intramolecular chaperone art generally. This reference concerns subtilisin, a very large enzymatically active protein whose folding is facilitated by an intramolecular chaperone prosequence. Inouye teaches how to identify the functional domains of an intramolecular chaperone necessary for folding, and exemplifies the mutational method for generating and testing intramolecular chaperone variant polypeptides. Inouye is interested in mapping the domains of the intramolecular chaperone important to intramolecular chaperone function. Inouye gives emphasis to the effect of amino acid substitutions and deletions on the functionality of intramolecular chaperones not to show operable mutations are improbable or uncommon as the Office Action would have it, but rather to prove that the N-terminal portion of the pro-subtilisin operates as an intramolecular chaperone by disrupting its function. He also uses the mutations to indicate the location of the domains of the intramolecular chaperone peptidyl fragment that are important to its operability. In contrast to the Examiner's use of the reference, Inouye also unequivocally sets forth that the there are a great many mutations that would preserve the intramolecular chaperone function. In fact, Inouye states at col. 5, third full paragraph:

> The identification method can be so conducted to determine one or more functional domains responsible for folding the inactive polypeptide into a biochemically active conformation. Substitutions of functionally equivalent amino acids can be performed in the identified domain(s) and the resulting peptide tested in accordance with the identification method. Peptides can thus be made which are still effective to activate the polypeptide but contain no amino acid residue(s) which is identical to that of the native pro-sequence.

Indeed, the Inouye patent issued with the following base claim which is considerably broader with respect to both its intramolecular chaperone subject matter and its folded peptide subject matter:

> 1. An in vitro method to restore or increase the natural biological activity of a target polypeptide, which is normally expressed containing a prosequence, which target polypeptide is biologically inactive or has decreased natural biological activity due to improper folding of the polypeptide, which method comprises reacting intermolecularly in a buffered ionic aqueous medium, thereby favoring hydrophobic interaction, an exogenous activating peptide with the target polypeptide, *wherein the activating peptide has the amino acid sequence of the prosequence of the target polypeptide or of a polypeptide which has the same function as the target polypeptide and which is similar in amino acid sequence to the target polypeptide,* whereby the activating peptide promotes refolding the target polypeptide into its biologically active conformation.

[Italics added for emphasis.] Independent claims 15 and 22 of the Inouye reference are also similarly broad with respect to their intramolecular chaperone subject matter.

(vii) Predictability of the Art.

In contrast, MPEP §2164.03 titled "Relationship Between Predictability in the Art and the Enablement Requirement" sets forth that "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the *disclosed* or known results to the claimed invention." [italics added for emphasis] (see p. 2100-182, second full paragraph first column). Applicants have *disclosed* the new property of the first peptidyl fragment as being a suitable intramolecular chaperone for folding an insulin precursor fragment. In view of the above-discussed state of the art, Applicants submit that one of ordinary skill in the art could extrapolate

the disclosed results concerning the intramolecular chaperone properties of the first peptidyl fragments as set forth in the base claims of the instant application.

In support of the contention that the relevant art is unpredictable, the Examiner cites both Inouye references (i.e., U.S. Patent No. 5,719,021 and Inouye, Enzymes 45:314-321 (1991)) as disclosing inoperable subject matter. Both Inouye references can be cited to illustrate mutations and truncations in an intramolecular chaperone that can eliminate its intramolecular chaperone activity with respect to the target peptide. The Examiner cites Inouye as disclosing that deleting the first 15 or 43 amino acids of their intramolecular chaperone eliminates the chaperone function. The Examiner also cites Inouye as disclosing that many amino acid sequence substitutions within the intramolecular chaperone can eliminate its chaperone activity. However, Applicants note that according to the MPEP §2164.08, the standard of patentability is not whether any inoperable subject falls within the scope of a claim:

> **2164.08(b) Inoperative Subject Matter**
> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

The test of enablement is rather on whether one of ordinary skill in the art would have to perform *undue* experimentation in order to practice the claimed invention. In this regard, Inouye does not stand for the proposition that there are no operable intramolecular chaperone variants in his system. While Inouye may have focused on inoperable subject matter so as to prove the role of the intramolecular chaperone and to identify its critical domains, Inouye actually taught that there were many operable intramolecular chaperone variants for subtilisin:

> In studies with subtilisin (but not limited thereto), pro-peptides which are synthetic as opposed to the native pro-sequence, have been shown to contribute to the folding of the peptide to an active conformation by an intermolecular reaction. The amino acid constitution and/or sequence of the amino acid residues of the activating peptide need not be the same as that of the native pro-sequence. It is generally

> sufficient that it be in part the same as that of the native pro-sequence in that it contains one or more of the identified functional domains to cause the inactive polypeptide to be activated biochemically.

(Inouye U.S. Patent No. 5,719,021 at col. 5, 2nd full paragraph). Indeed, Inouye pursued and was granted correspondingly broad claims as discussed above.

Inouye went much further to show that one can even obtain compensating amino acid substitutions at a second site in the polypeptide amino acid portion of the *target* which offset a mutation in the intramolecular chaperone portion of the molecule so as to restore both intramolecular chaperone activity and the correct folding. Thus, Inouye demonstrates that a very high state of the art exists in so far as he was able to modify both the intramolecular chaperone portion and the target to provide a coordinated set of mutations.

In short, Inouye simply does not support the proposition the Examiner would find there.

viii. Quantity of Experimentation Necessary.

The field of the invention is the pharmaceutical arts. A great deal of experimentation is quite routine in this field. It is a field which is largely devoted to the screening and testing of a large number of candidate compounds, compositions and treatments in model systems[2]. Indeed, Wands itself is evidence that a great deal of screening activity if routine is no bar to enablement. In addition, clinical testing is not required to demonstrate the clinical utility of the product. Correctly folded insulins are among the oldest and best known of the peptide hormones.

In fact, very little additional experimentation would be required to practice other embodiments of the invention. With respect to variant first peptidyl fragments of less than 48

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[2] Indeed, The Federal Circuit has held that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988).

amino acids in length, the Applicants have filed a declaration in the parent application setting forth that a 40 mer is an effective intramolecular chaperone for an insulin precursor and that an 18-mer is inoperable. To avoid any inoperable truncations occurring over the 22 amino acid span of the difference between these two lengths, one of ordinary skill in the art would only need to make and test only a handful of such variants to determine the minimum length needed for operability. With respect to variant first peptidyl subject matter having one or two amino acid substitutions, such subject matter is readily ascertainable by one of ordinary skill in the art and could be readily achieved by substitution of one like amino acid for another (acid for acid, base for base, hydrophobic for hydrophobic, etc.). As discussed above, Inouye teaches that one of ordinary skill in the art could readily obtain *operable* limited variants of such intramolecular chaperone sequences.

Accordingly, the Applicants believe that their disclosures and the art already of record fully enable the first peptide fragment subject matter as now set forth in the claims.

The second peptide fragment/Human insulin precursor peptide fragment

Turning now to the second peptide fragment comprising a "human insulin precursor," without acquiescing to the position of the Examiner, the Applicants have amended the base claim to recite:

> a human insulin precursor peptide fragment consisting of the B and A chains of human insulin wherein the B and A chains are separated by removable connecting moiety, wherein the removeable connecting moiety consists of an amino acid residue or a peptide fragment consisting of 2 to 34 amino acid residues;

Hence, the subject matter of the human insulin precursor now limits the sequences of the B and A chains to the corresponding human sequences. The subject matter of the connecting moiety finds support in the specification which incorporates by reference several references which are already of record. In particular, Thim *et al.,* PNAS 83:6766-6770 (1986) disclose insulin precursors having a removeable linking moiety of from 2 to about 34 amino acids in length (see p. 6768, the paragraph bridging columns and Table 1). In addition, U.S. Patents Nos. 5,473,049 and 5,457,066, which were incorporated by reference and are also already of record, similarly

disclose and claims processes for making insulin precursor polypeptides having a removeable peptide moiety of from about 1 to 35 amino acids in length (see claim 1, Formula I) and which have the correctly linked cystine bridges.

Accordingly, the Applicants believe that their disclosures and the art already of record fully enable the "human insulin precursor" subject matter as now set forth in the amended claims.

Overall Summary of the Wands Analysis

Here,

(i) the relative skill and experience of those in the relevant fields of recombinant protein expression and peptide synthesis is high.

(ii) the nature of the invention is in the manufacture of correctly folded insulin peptides using intramolecular chaperones; the contested subject matter concerns amino acid sequence and length variants of intramolecular chaperones.

(iii) the breadth of the claims, as amended, is fully commensurate with the specification disclosure, in particular, in view of the previous amendments, a greatly reduced number of possible variants of first peptidyl fragments are involved;

(iv) the specification provides adequate guidance for all manipulations required to practice the invention;

(v) the specification provides working examples; the declaration sets forth a 40 amino acid long first peptidyl fragment is operable and that an 18 amino acid long first peptidyl fragment was inoperative.

(vi) the state of the art is high as exemplified by the work of Inouye.

(vii) the art is sufficiently predictable such that one of ordinary skill in the art could practice subject matter within the scope of the claimed subject matter without undue experimentation; here, the Applicants have readily shown two embodiments of such are operable.

(viii) while the field of art is one in which a great deal of experimentation is routinely performed by a person of ordinary skill in the art, in fact relatively little additional research would be required to practice the invention.

In view of the above amendments to the claims, specificationtion, and *Wands* analysis, Applicants believe that one of ordinary skill in the art could readily practice the invention as claimed using an amount of experimentation which would be clearly routine in the art. Applicants therefore request that the above rejection be reconsidered and withdrawn.

Response to the Rejection of Claims 98 to 104, 109 to 111, 114 to 124, 129 to 131 and 134 to 144 as allegedly not satisfying the written description requirement pursuant to 35 U.S.C. §112, first paragraph.

Applicants have amended the base claim to recite:

> A recombinant nucleic acid encoding a chimeric protein, the chimeric protein comprising:
> a first peptide fragment of from 20 amino acids in length to 92 amino acids in length and having an amino acid sequence which is identical to an N-terminal amino acid sequence of SEQ ID NO: 2 of the same length as the first peptide fragment or having an amino acid sequence which differs by one or two residues from the N-terminal sequence of SEQ ID NO:2 of the same length as the first peptide fragment;
> a human insulin precursor peptide fragment consisting of the B and A chains of human insulin wherein the B and A chains are separated by removable connecting moiety, wherein the removeable connecting moiety consists of an amino acid residue or a peptide fragment consisting of 2 to 34 amino acid residue; and
> an arginine amino acid residue, a lysine amino acid residue, or at least one cleavable peptide fragment linking the first and human insulin precursor peptide fragments;
> wherein the first peptide fragment is capable of mediating, upon contacting of the chimeric protein with a chaotropic agent, the formation of a correctly folded conformation of the human insulin precursor peptide fragment.

Turning to the first peptide fragment, the Applicants note that this fragment is now more closely defined according to the amino sequence of SEQ ID No.:2 and can differ from a corresponding portion thereof by at most <u>two</u> amino acid residues. The recital of "having

sufficient homology" to which the Examiner was adverse has been accordingly deleted. Applicants note further that the 'genus' is now much tighter that one of ordinary skill in the art would readily appreciate (especially, in light of the many conservative amino acid substitutions possible) that the disclosed species is well representative of the subgenus now set forth in the claim.

Turning to the human insulin precursor peptide fragment, Applicants first note that the human B and A chain subject matter is now drawn to the human sequences thereof and that the removeable connecting moiety therebetween has been further specified. Additionally, as noted earlier, the Applicants have amended the specification to add removeable connecting moiety subject matter which was previously incorporated by reference. Additional such subject matter is also disclosed in Thim *et al.*, as discussed above, and which was also incorporated by reference. Accordingly, Applicants believe that the written description of this subject matter is also fully supported by the specification. Thus, the Applicants respectfully request that the above rejection be reconsidered and withdrawn.

Response to the rejection of claim 98 for alleged indefiniteness in view of the recital of "the bioactive conformation."

As amended, the base claim no longer recites "the bioactive conformation." The base claim now recites "correctly folded conformation of the human insulin precursor peptide fragment." This subject matter is defined in the specification at p. 24, last full paragraph. Accordingly, the Applicants respectfully request the above rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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